

HLH-94: A Treatment Protocol for Hemophagocytic Lymphohistiocytosis

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INTRODUCTION

In January 1995, the Hemophagocytic Lymphohistiocytosis (HLH) Study Group opened its first international treatment study dedicated to the hemophagocytic lymphohistiocytoses. The main intention of the study protocol is to offer affected children therapy with a well-established chemotherapeutic regimen (epipodophylotoxin and corticosteroids) *in combination* with a newer approach, immunotherapy with cyclosporin A. Subsequent bone marrow transplantation (BMT) is recommended to all children with an available donor. The purpose of this communication is to describe this approach to management, that intends to prolong survival and increase the cure rate for children throughout the world with this highly lethal disease [1].

Nomenclature

The term histiocytoses encompasses a group of disorders that have in common lesions that feature cells of the mononuclear phagocyte system and/or dendritic cells. The non-malignant histiocytoses can be divided into: (1) disorders mainly affecting the (primarily antigen-presenting) dendritic cells, with Langerhans cell histiocytosis (LCH) being the most common disease; and (2) disorders mainly affecting the ordinary (primarily antigen-processing) macrophages. Here hemophagocytic lymphohistiocytosis (HLH) is the most common disease [2].

Hemophagocytic lymphohistiocytosis comprises two different conditions which may be difficult to distinguish from each other [2,3]:

(i) *Primary hemophagocytic lymphohistiocytosis* (familial or sporadic)

A hereditary transmitted disorder, considered as an autosomal recessive disease, affecting the immune regulation. Although it is commonly termed *familial hemophagocytic (erythrophagocytic) lymphohistiocytosis* (FHL, FEL, or FHLH), since the disease is recessive, it often appears as a sporadic case with a negative family history.

It is of utmost importance to be aware that FHL may

also be elicited by, or associated with, infections. This means that the presence of an infection in a child with HLH may also be a concomitant finding that does not rule out an inherited disease, i.e. primary HLH (FHL).

(ii) *Secondary hemophagocytic lymphohistiocytosis*

A lymphohistiocytic proliferation with hemophagocytosis may also develop from strong immunological activation, mainly of the mononuclear phagocyte system, such as a severe infection (*infection-associated hemophagocytic syndrome*) (IAHS). The condition has been described in immunocompromised hosts in association with viral infections and the term *virus-associated hemophagocytic syndrome* (VAHS) is also frequently used [4]. Bacteria and parasites may also induce secondary HLH [3]. The syndrome may also develop subsequent to other forms of immunological stress and activation, such as during malignancies (*malignancy-associated hemophagocytic syndrome*, MAHS) or following prolonged intravenous nutrition including administration of soluble lipids (fat overload syndrome) [3].

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DIAGNOSIS AND CLINICAL PRESENTATION

Natural history

The incidence of primary HLH has been estimated to 1.2 per million children per year, which is equivalent to around 1 in 50,000 live-born children [1]. The disease is uniformly fatal without treatment. Previous studies have reported a median survival of two months from the time of diagnosis [1]. Of the first 122 patients reported to the Histiocyte Society's FHL Registry, only 27 were alive by November 1993 [5]. Ten of these patients received chemotherapy alone and 17 also received BMT. The estimated overall five-year survival rate was 17%.

Regarding secondary HLH, it is our impression that the disease is underdiagnosed since treating physicians do not often consider it in the differential diagnosis of candidate patients [6].

Clinical and laboratory features

The most typical presenting signs and symptoms of primary HLH are fever, hepatosplenomegaly, and cytopenias. Less frequently observed clinical findings are neurological symptoms, lymphadenopathy, edema, skin rash, and jaundice [1,5,7].

Common laboratory findings include hypertriglyceridemia, a coagulopathy with hypofibrinogenemia and liver dysfunction marked by elevated transaminase levels. The neurological symptoms are sometimes, but not always, associated with a moderate mononuclear cell pleocytosis and elevated cerebrospinal fluid protein.

Other abnormal findings of laboratory tests, some of which are not generally available in clinical laboratories, include: low natural killer (NK) cell activity [8–11], hyperferritinemia [12], increased very-low density lipoproteins and decreased high-density lipoproteins [13], and elevated cytokines in serum and CSF [14–18].

Histopathological examination of affected tissues such as lymph nodes, spleen, bone marrow, and liver, show widespread accumulation of cytologically normal hemophagocytic macrophages, and lymphocytes [3,7,19–20]. In the liver, a histological picture similar to chronic persistent hepatitis is commonly found.

Differential diagnoses

Malignancies such as leukemia and lymphoma are often suspected prior to biopsy. Benign conditions such as other histiocytoses and infectious diseases may also give similar clinical pictures.

Special difficulty is encountered distinguishing primary HLH from X-linked lymphoproliferative syndrome (XLP) and, in non-familial cases, the primary form of HLH from secondary forms [3,21]. Patients with XLP frequently manifest an EBV-related hemophagocytic process as the terminal feature of their disease. Recent

TABLE I. Diagnostic Guidelines for HLH* (adapted from ref 3)

Clinical criteria

- * Fever
- * Splenomegaly

Laboratory criteria

- * Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood:
 - Hemoglobin (<90 g/L)
 - Platelets ($<100 \times 10^9/L$)
 - Neutrophils ($<1.0 \times 10^9/L$)
- * Hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides ≥ 2.0 mmol/L or ≥ 3 SD of the normal value for age, fibrinogen ≤ 1.5 g/L or ≤ 3 SD)

Histopathologic criteria

- * Hemophagocytosis in bone marrow or spleen or lymph nodes.
- No evidence of malignancy

*All criteria required for the diagnosis of HLH. In addition, the diagnosis of FHL is justified by a positive family history, and parental consanguinity is suggestive.

Comments

1. If hemophagocytic activity is not proven at the time of presentation, further search for hemophagocytic activity is encouraged. If the bone marrow specimen is not conclusive, material should be obtained from other organs, especially lymph nodes or spleen (fine needle aspiration biopsy). Serial marrow aspirates over time may also be helpful.
2. The following findings may provide strong supportive evidence for the diagnosis:
 - (a) Spinal fluid pleocytosis (mononuclear cells),
 - (b) Histological picture in the liver resembling chronic persistent hepatitis,
 - (c) Low natural killer cell activity.
3. Other abnormal clinical and laboratory findings consistent with the diagnosis are: Cerebromeningeal symptoms, lymph node enlargement, jaundice, edema, skin rash. Hepatic enzyme abnormalities, hyperferritinemia, hypoproteinemia, hyponatremia, spinal fluid protein \uparrow , VLDL \uparrow , HDL \downarrow , circulating soluble IL-2 receptor \uparrow .

studies have defined an EBV-related clonal disease in a patient with HLH without apparent lymphoma formation. It is unclear whether that patient suffered from a T-cell or NK-cell malignancy [22].

Diagnostic guidelines

There is no specific feature of primary HLH. The diagnostic guidelines that were developed by the HLH Study Group in 1991 are summarized in Table I [3]. The criteria include clinical, laboratory, and histopathological findings. There is increasing evidence that not all cases of clearly familial disease fulfill all the diagnostic criteria. Moreover, a number of patients may express one or more of the diagnostic criteria *late* in the course of the disease [3,5,23]. **Thus, in the absence of any specific marker of disease, treatment may start on the basis of a strong clinical suspicion of primary HLH**, before overwhelming disease activity makes irreversible damage and the chances of response to treatment less likely. (Treating physicians who have questions should contact the local subcenter.)

As previously discussed, it may be difficult to distinguish primary HLH from secondary on the basis of clinical and histological information. A positive family history or parental consanguinity strongly suggests primary HLH; i.e. FHL.

Most often primary HLH presents during the first two years of life. The oldest patient so far in the FHL Registry with verified familial disease was seven years of age at first presentation. An associated infection does not rule out primary (familial) HLH since this disorder may be elicited by infections [5,24].

Natural Killer and T-cell Cytotoxic Activity

We postulate that the signs and symptoms of primary HLH are due to hyperactivity of macrophages and T-lymphocytes. The cause of this inappropriate immune activation in HLH is not known. It has, however, been shown that the NK cytotoxic activity is markedly decreased in children with primary HLH [8–11], as is T-cell cytotoxic function [25]. Since it is not known whether these effects are primary or secondary, we aim to elucidate this question in the course of this study.

Analyses of NK-cell activity and T-cell cytotoxic activity are recommended *prior to treatment* and after six and twelve months of treatment and prior to BMT. Selected laboratories are available in different geographic regions; see below.¹

THERAPEUTIC BACKGROUND

Systemic therapy

Without treatment, the disease is usually rapidly fatal and has a median survival of two months [1]. Prior to the introduction of the epipodophyllotoxins, vinblastine and corticosteroids were the most effective treatments available [7]. Repeated plasma or blood exchange also induced resolution in some patients [26]. Prolonged remission was first achieved with the introduction of etoposide (VP-16) [27] and later, teniposide [28] in combination with steroids.

Recent reports have emphasized the risk of secondary leukemia (non-lymphoblastic) and myelodysplastic syndrome following the use of epipodophyllotoxin derivatives [29]. Out of the first 122 patients included in the FHL Registry, only one child developed such a complication. This patient is still alive following BMT [30].

Although the risk of secondary leukemia is quite small in comparison with the fatality rate of the disease, we

intend to reduce the risk even further by reducing the total VP-16 dosage. This is achieved by using a combination of chemotherapy and immunotherapy in this protocol.

Recent studies have reported the usefulness of immunotherapy with Cyclosporin A in primary HLH [31,32]. Antithymocyte globulin has been successful in inducing resolution of the disease [31]. The concurrent use of immunotherapy (Cyclosporin A) in HLH-94 is also intended to further stabilize the continuation therapy.

Central nervous system therapy

Primary HLH may cause severe and irreversible CNS damage [23, 33]. Intrathecal methotrexate and cranial radiation were initially added to an epipodophyllotoxin-steroid regimen [34]. Later regimens retained the intrathecal therapy but eliminated the radiation [35]. Clinical observations by members of the HLH Study Group indicate that CNS activation often resolve with effective systemic therapy and that intrathecal therapy alone is not particularly effective. Steroids, however, are known to effectively penetrate the blood-brain barrier. Therefore, the first line of systemic therapy in this protocol includes high dose dexamethasone and reserves intrathecal therapy for those patients with clinical evidence of CNS progression or unimproved CSF pleocytosis.

Bone marrow transplantation

A major therapeutic breakthrough was achieved with the introduction of allogeneic BMT, which not only leads to prolonged disease control, but also cure [36–42]. Today, allogeneic BMT is considered the treatment of choice, especially when a closely HLA-matched donor is available.

The initial outcomes with mismatched related donors and matched unrelated donors were not as satisfactory as with a matched family donor [38]. Results from the United States National Marrow Donor Program show a 43% actuarial survival rate at 2 years following unrelated BMT [Dr. Filipovich, Cincinnati, pers. comm.].

Since chemotherapy has not been shown to cure children with the familial form of the disease, BMT from donors other than matched related siblings is being increasingly performed throughout the world, and is included as part of this study protocol.

STUDY DESIGN

Protocol strategy

To assist clinicians who see only a rare case, the HLH-94 protocol includes an initial diagnostic approach as well as a therapeutic strategy. We emphasize that this is a *research* protocol and urge all physicians to follow their institutional ethics guidelines and register all pa-

¹ Recommended laboratories for analyses of NK-cell activity and T-cell cytotoxic activity: America (incl Canada and Latin America): Minneapolis - Dr. Filipovich; tel lab +1-612 624 7686, fax 612 624 9672; Asia: Tokyo - Mr. Koji Iwaki, SRL Inc.; tel +81-426-48-4085 or 426-46-5911; Europe: Düsseldorf - PhD E. M. Schneider; tel +49-211 311 8577, fax 211 311 6221

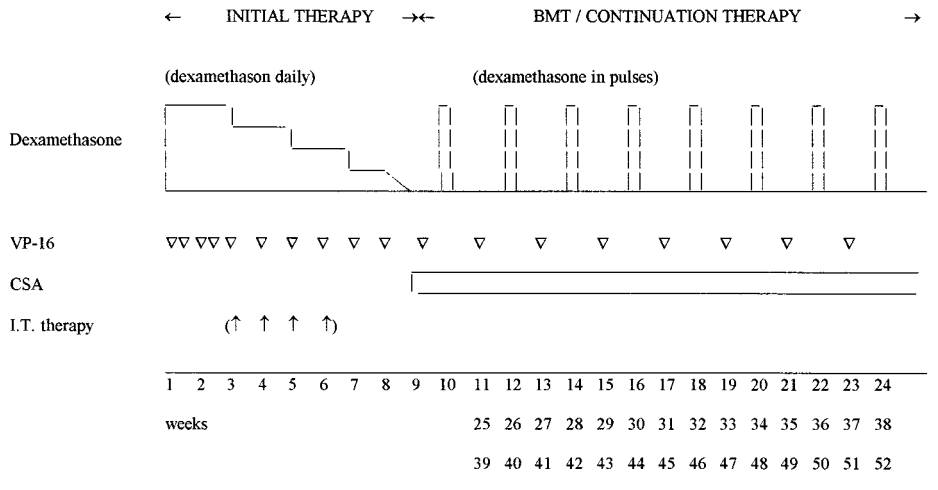


Fig. 1. Schematic overview of the treatment protocol for hemophagocytic lymphohistiocytosis (HLH-94).

tients with the regional study coordinator. See correspondence. For general overview, see Figure I.

The initial therapy, aiming at inducing a resolution of the disease, includes etoposide, steroids and, in selected patients, intrathecal methotrexate. The intention of the continuation therapy, which also includes Cyclosporin A, is to maintain a stable resolution of the disease in order to be able to cure by BMT if an acceptable donor is available.

Patient's eligibility

All children aged 15 years or less are eligible for registration if the following criteria have been met:

- (1) Patient fulfills the diagnostic criteria of HLH, (see also the chapter 'diagnostic guidelines').
- (2) No prior treatment with chemotherapy or Cyclosporin A for the treatment of HLH. Prior steroid treatment is acceptable, as is plasmapheresis.

TREATMENT

Supportive care

It should be anticipated that these patients, if not already so, may become critically ill. Treating physicians should plan for maximal supportive care:

- *Pediatric Intensive Care Unit if appropriate
- *Broad-spectrum antibiotics until culture results are available
- *Close microbiological surveillance during therapy
- *HLA typing of patient and family as early in course as possible
- *Prophylactic cotrimoxazole (5 mg/kg of trimethoprim equivalent), three times weekly
- *An oral antimycotic during initial dexamethasone phase

Chemotherapy and immunotherapy

A schematic overview of the treatment protocol, presented in Figure 1, summarizes the pre-BMT phase. Copies of the entire protocol with detailed dosage information are available from the local study centers to interested physicians (see correspondence section).

Bone marrow transplantation

If available, an HLA-identical relative is preferable as donor. The risk that a sibling may be carrying the disease must be considered. This is less likely if an older sibling is used. BMT can still be considered with a less-matched related or unrelated donor at the discretion of the treating physicians.

The preparative treatment for BMT and regimen for graft-versus-host disease (GVHD) prophylaxis is determined by the treating physician and local BMT unit. At present, however, we would advise including VP-16, busulfan and cyclophosphamide in the conditioning regimen, in accordance with the experience in Paris [38], Pavia [39], Minneapolis [40], and Stockholm [41].

CONCLUSION

Hemophagocytic lymphohistiocytosis is a rare disease with a very high mortality. A protocol has been developed by an international group of clinicians experienced in the treatment of children with HLH. The wide participation of pediatric treatment centers in the study of this disease will ensure that children throughout the world have access to a state of the art treatment. The HLH Study Group needs the cooperation of every physician who treat patients using the HLH-94 protocol to evaluate the usefulness and safety of this protocol. Furthermore, by combining our patient resources, information can be

more easily gathered, which will benefit future generations of patients.

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